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EXAMINER
COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/836,548	Applicant(s) DREWE et al.
	Examiner Brenda Coleman	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 15, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-93* is/are pending in the application.

4a) Of the above, claim(s) *15-21 and 41-46* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14, 22-40, and 47-93* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-93 are pending in the application.

Election/Restriction

1. Applicant's election with traverse of Group I in Paper No. 6 is acknowledged. The traversal is on the ground(s) that there would be no undue burden on the Examiner to consider all of the claims. This is not found persuasive because the compounds represented by the Groups I, II, III and IV are of a different core which are separately classified. A search on a thiazepine is not the same as a search on the benzothiazepine of Group II, the benzodiazepine of Group III or the 2,5-dioxa-9-thia-6a-aza-cyclohepta[a]naphthalene-1,6-dione ring of Group IV. The degree of burden in searching the compounds of the instant invention is high. To illustrate the extent of the burden present on the examiner to perform a thorough search, the number of patents present in a search conducted on the elected group where A^2 is a thiazepine containing moiety in the compounds of Formula I is 758 U.S. patents at this time. This does not include the added search of foreign patents or chemical literature.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 15-21 and 41-46 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6.

3. Claims 1-5, 35, 49-64, 66-73, 75-83 and 85-93 are rejected as being an improper Markush grouping. The recited compounds, while possessing a common utility, present a variable core and, thus, the Markush group represented by the term ~~L in formula I and n in formula A~~ X' and ring A^2 have variably different definitions, rendering the claims clearly improper.

BF 1-15-03

Information Disclosure Statement

4. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-14, 22-40, 47-50 and 52-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of "prodrug" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of a "prodrug"

will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrug will be suitable for the instant invention.

6. Claims 54-56 and 66-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of the method claims are not adequately enabled solely based on the activity of progesterone provided in the specification. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds *In re Buting* 163 USPQ 689. The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "tumor" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task.

Instant claim language embraces disorders not only for treatment but for **prevention** which is not remotely enabled. It is presumed in the prevention of the diseases and/or disorders claimed herein there is a way of identifying those people who may develop cancer. There is no

evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders claimed herein.

There never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to treat cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of *in vivo* efficacy by those skilled in the art. See *In re Ruskin*, 148 USPQ 221; *Ex parte Jovanovics*, 211 USPQ 907; MPEP 2164.05(a).

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ

of an idea does not constitute enabling disclosure. *Genentech Inc. v. Novo Nordisk* 42 USPQ2d 1001.

7. Claims 55, 56, 85 and 86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The registered trademarks used as reducing agents is not described in the specification. The relationship between a trademark and the product it identifies is sometimes indefinite, uncertain, and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark. In patent specifications, every element or ingredient of the product should be set forth in positive, exact, intelligible language, so that there will be no uncertainty as to what is meant. See MPEP 608.01(v).

8. Claims 57-65 and 89-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of claims 57-65 and 89-93 are not adequately enabled solely based on a disorder responsive to the induction of apoptosis, provided in the specification. Claims 57-65 and 89-93 are the method of treating any and all diseases and/or disorders associated with the induction of apoptosis, which is not remotely enabled. The scope of claims 57-65 and 89-93

includes diseases and/or disorders not even known at this time which may be associated with the induction of apoptosis.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-14, 22-40 and 47-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1-14, 22-40 and 47-93 are vague and indefinite in that it is not known what is meant by the definition of the substituents on "each ring within A^1 and R^{5n}". It is not known whether this is a further definition of A^1 where A^1 contains from 3 to 8 ring atoms and which may be substituted with 1 to 3 groups independently selected form (C_{1-6})alkyl, cyano, ... in addition to the substituents already defined for A^1.

b) Claims 1-7, 9, 11, 13, 22-24, 26, 28, 29, 31, 33, 35-37, 39, 49-61, 66-70, 75-80, and 85-93 are vague and indefinite in that it is not known what is meant by the two different definitions for the variable R^9.

c) Claims 1-14, 22-40 and 47-93 are vague and indefinite in that it is not known what is meant by the definition of the substituents on "each ring within A^2 and R^{8n}". It is not known whether this is a further definition of A^2 where A^2 contains from 3 to 8

ring atoms and which may be substituted with 1 to 3 groups independently selected form (C_{1-6})alkyl, cyano, ... in addition to the substituents already defined for A^2.

d) Claims 1-14, 22-40 and 47-93 are vague and indefinite in that it is not known what is meant by the definition of the substituents on "each ring within A^3 and R^{10}". It is not known whether this is a further definition of A^3 where A^3 contains from 3 to 8 ring atoms and which may be substituted with 1 to 3 groups independently selected form (C_{1-6})alkyl, cyano, ... in addition to the substituents already defined for A^3.

e) Claims 1-14, 22-40 and 47-93 are vague and indefinite in that it is not known what is meant by *N*-oxide **derivatives**, prodrug **derivatives**, or protected **derivatives**. "Derivative" implies more then what is positively recited.

f) Claims 1, 57-59, 66-68 and 76-78 recite the limitation "**4-hydroxy-6-methyl-2-oxo**-2H-pyran-3-yl" in structure of Formula II(a). There is insufficient antecedent basis for this limitation in the claim.

g) Claim 1 recites the limitation "mono-substituted by fluoro, bromo, iodo, nitro, methyl, isopropyl, ethoxy or methylsulfanyl" in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

h) Claim 1 recites the limitation "substituted by at least one of chloro, hydroxy or methoxy" in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

i) Claim 2 recites the limitation "substituted by at least one of halogen, nitro, hydroxy (C_{1-6})alkyl, methoxy, ethoxy and methylsulfanyl" in proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

j) Claim 2 recites the limitation "halogen and (C_{1-6})alkyl" in proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

k) Claim 3 recites the limitation "**4-hydroxy-6-methyl-2-oxo**-2H-pyran-3-yl" in the proviso. There is insufficient antecedent basis for this limitation in the claim.

l) Claims 7, 24, 29, 37 and 39 recite the limitation "**4-hydroxy-6-methyl-2-oxo**-2H-pyran-3-yl or **4-methoxy-6-methyl-2-oxo**-2H-pyran-3-yl" in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim.

m) Claims 9 and 31 recite the limitation "**4-hydroxy-6-methyl-2-oxo**-5,6-dihydro-2H-pyran-3-yl or **4-methoxy-6-methyl-2-oxo**-5,6-dihydro-2H-pyran-3-yl" in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim.

n) Claims 11 and 33 recite the limitation "**2-hydroxy-6-oxo**-cyclohex-1-enyl or **2-methoxy-6-oxo**-cyclohex-1-enyl" in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim.

o) Claim 13 recites the limitation "**R^{11} substituted 4-hydroxy-2-oxo**-quinolinyl or **4-methoxy-2-oxo**-quinolinyl" in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim.

p) Claim 14 is vague and indefinite in that the nomenclature is missing an open parenthesis.

q) Claim 35 recites the limitation "n" in the compound of Formula I(G). There is insufficient antecedent basis for this limitation in the claim.

r) Claims 35 and 36 are vague and indefinite in that it is not known what is meant by the definition of n which is as defined in Claim 1.

s) Claims 36-40 recite the limitation "n" in the compound of Formula (l). There is insufficient antecedent basis for this limitation in the claim.

t) Claim 48 is vague and indefinite in that it is not known what is meant by the second period at the end of the claim.

u) Claims 49, 60, 69 and 79 recite the limitation "substituted pyran, quinoline, cyclohexenyl and phenyl" in the definition of A^1. There is insufficient antecedent basis for this limitation in the claim.

v) Claims 49 and 51 recite the limitation "heteroalkylene" in the definition of R^6. There is insufficient antecedent basis for this limitation in the claim.

w) Claims 52, 60, 69 and 79 recite the limitation "n" in the compound of Formula (l). There is insufficient antecedent basis for this limitation in the claim.

x) Claims 52-56 recite the limitation "prodrug" in the compound of Formula II. There is insufficient antecedent basis for this limitation in the claim.

y) Claims 57, 66 and 76 recite the limitation "mono-substituted by bromo, hydroxy, methyl or isopropyl" in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

z) Claims 57, 58, 66, 67, 76 and 77 recite the limitation "substituted by at least one of Cl and methoxy and not substituted by methylsulfanyl, amino, methylamino and dimethylamino" in proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

aa) Claims 58, 67 and 77 recite the limitation "mono-substituted by bromo, nitro, hydroxy, methyl or isopropyl" in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

ab) Claims 58, 59, 67, 68, 77 and 78 recite the limitation "nitro" in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

ac) Claims 59, 68 and 78 recite the limitation "substituted by at least one of bromo, chloro, hydroxy, nitro, methoxy and (C_{1-3})alkyl" in the proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

ad) Claims 59, 68 and 78 recite the limitation "(C_{1-3})alkyl" in proviso with respect to the definition of A^3. There is insufficient antecedent basis for this limitation in the claim.

ae) Claims 63, 72 and 82 are vague and indefinite in that it is not known what is meant by thizepan in the third species on page 130 and 143, respectively.

af) Claims 63, 72 and 82 are vague and indefinite in that the nomenclature of the species spanning lines 15-16 on page 132 and 145 and lines 25-26 on page 158, respectively are missing an open parenthesis.

ag) Claim 57-65 and 89-93 is vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are responsive to the induction of apoptosis. Determining whether a given disease responds or does not respond to the induction of apoptosis will involve undue experimentation. Suppose that a given drug, which has inductive properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One can not conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given

drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration can not be predicted in advance. Should our drug be given as a bolus *iv* or in a time release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inductives of apoptosis must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are inductive *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property which the second drug is capable. It is common for a drug, particularly in antiinflammatory, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

ah) Claim 75 is vague and indefinite in that it is not known what is meant by "skin cancer an prostatic carcinoma" in the last line of the claim.

ai) Claim 78 is vague and indefinite in that it is not known what is meant by (C_{1-3})alky.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 1-7, 9, 11, 13, 22-24, 26, 28, 29, 31, 33, 35-37, 39, 49-61, 66-70, 75-80, and 85-93 are rejected under 35 U.S.C. 102(a) as being anticipated by Stockwell et al., WO 00/07017. Stockwell teaches the compounds of the instant invention as shown in the CAPLUS printout herein provided.

Claim Objections

Claims 5, 6, 22, 28, 36 (and claims dependent thereon) are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be in the alternative. See MPEP § 608.01(n).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner

can normally be reached on Mondays from 8:30 AM to 5:00 PM, on Tuesdays from 8:00 AM to 4:30 PM, on Wednesday thru Friday from 9:00 AM to 5:30 PM..

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
Primary Examiner AU 1624
November 4, 2002